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EXAMINER
WALICKA, MALGORZATA A

ART UNIT	PAPER NUMBER
1652	18

DATE MAILED: 05/20/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/554,414	SZYF ET AL.	
	Examiner	Art Unit	
	Malgorzata A. Walicka	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 February 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *32-38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *32-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

The application is the national stage of the PCT/CA98/01059 application.

The Reply to the Office Action filed on February 19, 2003 as paper No. 17 is acknowledged. Amendments to the claims have been entered as requested. Claims 1-31 are canceled. New claims 32-38 are entered.

DETAILED ACTION

1. Election/Restriction

Applicant's election of Group XIII-2, which relates to the use of an antagonist or inhibitor of the human DNA demethylase of SEQ ID NO:2, amino acids residues 150-411, for restoring an aberrant methylation pattern in the patient DNA is acknowledged.

In response to the species election requirements Applicants elected the species of double stranded oligonucleotides and antisense oligonucleotides of DNA demethylase.

2. Priority

Acknowledgment is made of Applicants' claim for priority based on Canadian Patent No. 2,230,991, filed May 11, 1998.

3. Objections

3.1. Specification

The abbreviation MDB and MeCP2, page 9, line 12 should be expanded.

The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors in the specification of which applicant may become aware.

3.3. Drawings

This application has been filed with informal drawings which are acceptable for examination purposes only. Formal drawings will be required when the application is allowed.

4. Rejections

4.1. 35 USC section 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claim 38 is rejected under 35 U.S.C. 101 because the disclosed invention is inoperative and therefore lacks utility. The claim is directed to a method for correcting the genetic defect underlying beta-thalassemia and sickle cell anemia by changing the pattern of patient DNA methylation, wherein the change is caused by inhibition of DNA demethylase.

Genetic defects underlining the clinical syndrom called ß-thalassemia is complex. There are more than 200 mutation causing beta-thalassemia, see page 5 of the enclosed copy of "Inherited haemoglobin disorders: an increased global health problem", by Weatherhall D.J. et al., *Bulletin of World Health Organization*, 2001, 79, 704. 2001. The mutations are in the gene encoding beta globin. Sickle cell anemia is, on the other side, caused by a single mutation in the beta globin gene.

Because both disorders are caused by structural mutations in globin gene, changes in methylation status of said gene do not allow for correction of these genetic defects.

4.2. 35 USC, section 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claim 32-38 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims are unclear in reciting

(1) "restoring an aberrant methylation pattern ", claim 32,

(2) "small molecule", claim 35.

The terms (1) and (2) are not defined by the claim or the specification. It is unclear what Applicant mean by aberrant methylation pattern that is to be restored. Applicants do not define what a normal and abberant patterns are. It is also unclear what it means that abberant pattern is restored, because no criterion for this restoration is given in the specification. In addition, the language of claim is vague, because it is unclear as to the state to which the pattern is to be restored. Is it a normal pattern of a healthy person, or an undefined aberrant pattern?

Claims 33-38 are included in this rejection because they do not correct the language of the claim from which they depend.

Neither claim 35 nor the specification define what Applicants mean by small molecule. The term "small molecule" is very broad term comprising thousands of chemical compounds, and Applicants do not define which small molecules are included or excluded from the scope of the claim .

Claim 36 is unclear in reciting the method according to "one of claims 32". There is only one claim 32 in the application.

4.2. 35 USC, section 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which

it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4.2.1. Lack of written description

Claims 32-38 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are directed to a method for:

(1) treating cancer,

(2) restoring an aberrant methylation pattern in a patient DNA,

(3) changing methylation pattern in a patient DNA.

Applicants have failed to describe the claimed invention in such full, clear, concise and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention when the application was filed.

Federal Circuit states that the primary function of the written description requirement is to insure that an inventor had possession of the claimed subject matter and to allow one skilled in the art to recognize what is claimed. *See in re Blaser*, 556F.2d 534, 194 U.S. P. Q. 122(CCPA 1977), *Enzo Biochem*, 285 F. 3d 1013, 62 U.S.P.Q.2d 1289. The written description requirement is satisfied by the disclosure of

the claimed subject matter in such a descriptive means, *e.g.*, words, structures, figures and diagrams, to allow one skilled in the art to visualize or recognize the claimed subject matter, *Enzo Biochem.* 285 F. 3d 1013."

One skilled in the art is not able to visualize or recognize the invention because the claimed subject matter is not disclosed in such descriptive means as words, figures or diagrams presenting the recited biological phenomena and their changes. Given this complete lack of written description of any cancer to be treated, of any aberrant methylation pattern and its restoration, and any changing of any methylation pattern, one skilled in the art is not convinced that inventors had possession of the claimed invention at the time the application was filed.

In addition, claim 32 recites an antagonist or inhibitor of DNA demethylase. The terms antagonist or inhibitor are generic terms the scopes of which cover large and variable chemical compounds. The Applicants teach only following representatives of the claimed genus: oligonucleotide consisting of 4 units C^mG, wherein these four units maybe repeated several times, anti-DNA demethylase antibody, an antisense oligonucleotide of DNA demethylase and imidazol. In addition, the structure of the antisense oligonucleotide of DNA demethylase is not described in details, because the antisense vector of Fig. 15 is depicted schematically. This description is insufficient to give the identifying characteristics of all inhibitors as broadly recited by the claim. Given the lack of structural characteristics of additional representative species as encompassed by the claim, Applicants have failed to sufficiently describe the claimed

invention in such full, clear, concise and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention when the application was filed.

Claim 33 recites an antagonist that is a double stranded oligonucleotide that inhibits demethylase at K_i of 50 nM. Applicants disclose only 1 representative species of said genus whose structure is presented on page 7, line 32. This is however insufficient to give the identifying characteristics of all inhibitors as broadly recited by the claim. Given the lack of structural characteristics of additional representative species as encompassed by the claim, Applicants have failed to sufficiently describe the claimed invention in such full, clear, concise and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention when the application was filed.

Claim 35 is rejected because it recites limitation "a small molecule" that is not sufficiently described by the specification. The claim is directed to a large and variable genus of small molecules, however Applicants identify only one representant of said genus, a well known compound imidazole. This is insufficient to give the identifying characteristics of all small molecules as broadly recited by the claim. Given the lack of structural characteristics of additional representative species as encompassed by the claim, Applicants have failed to sufficiently describe the claimed invention in such full, clear, concise and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention when the application was filed.

Claim 37 is rejected because the disclosure fails to describe any genetic defect that is to be corrected. Claim 37 is directed to correction of a large and variable genus of genetic defects. However, Applicants fail to identify a single representative of said genus. Given the lack of identifying characteristics of genetic defect, as encompassed by the claim, Applicants have failed to sufficiently describe the claimed invention in such full, clear, concise and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention when the application was filed.

Claim 38 is directed to the correction of the genetic defect, which is named as ß-thalassemia. This description is not sufficient, because genetic defects underlining the clinical syndrom called ß-thalassemia is complex. There are more than 200 mutation causing beta-thalassemia, see page 5 of the enclosed copy of "Inherited haemoglobin disorders: an increased global health problem", by Weatherhall D.J. et al., Bulletin of World Health Organization, 2001, 79, 704, the basic information on thalassemias. Without identifying which genetic defect applicants mean, the claimed invention is not described in such full, clear, concise and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention when the application was filed.

4.2.2. Lack of enablement

Claim 32-38 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable

one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 32 is directed to a method for:

(1) treating cancer,

(2) restoring an aberrant methylation pattern in a patient DNA,

(3) changing methylation pattern in a patient DNA.

The specification, however, fails to teach

(1) which cancer to treat,

(2) what is an abberant methylation pattern and how to restore it,

(3) how to change the methylation pattern in a patient.

As Applicants fail to describe what is enumerated under (1)-(3); see the above rejection for lack of written description, to make and use the claimed invention necessisates undue experimentation. Factors to be considered in determining whether undue experimentation is required are summarized *In re* Wands [858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)]. The Wands factors are: (a) the quantity of experimentation necessary, (b) the amount of direction or guidance presented, (c) the presence or absence of working example, (d) the nature of the invention, (e) the state of the prior art, (f) the relative skill of those in the art, (g) the predictability or unpredictability of the art, and (h) the breadth of the claim.

The nature and breadth of the claimed invention encompasses:

(1) treatment of any cancer,

(2) restoration of any aberrant methylation pattern of DNA in any patient,

(3) changing the DNA methylation pattern in any patient.

The one skilled in the art realizes that mechanisms underlying cancerogenesis are versatile and not every cancer is caused by demethylation of cytosine in GC islands, which may lead to derepression of some genes involved in carcinogenesis. Therefore, one who would like to use demethylase inhibitors to treat cancer has to measure the level of the enzyme in all possible cancer and select as candidates for treatment only those types of cancers where production of DNA demethylase is increased in comparison with that of healthy people.

Regarding points (2) and (3) Applicant do not provide any teaching of what a normal and aberrant methylation patterns are, nor any guidance how to restore the aberrant pattern to the normal one or how to change the methylation pattern. There is now guidance as to the tissue from which the DNA is to be extracted nor how to visualize the pattern of DNA methylation. Applicants only provide the guidance how to measure the overall demethylase activity and not the pattern of DNA metylation. There is even not a single measurement of percentage of cytosine methylation for a single gene. Those skilled in the art know that the pattern of DNA methylation is

different in different genes, depending on the nucleotide sequence and the state of cell differentiation or its physiological state.

In conclusion, without further guidance on the part of Applicants as to the details regarding

(1) type of cancer to be treated,

(2) the measurement and visualization of methylation pattern,

(3) required change/restoration in the methylation pattern,

experimentation left to those skilled in the art has a low probability of success and is improperly extensive and undue.

Dependent claims 33-38 are included in this rejection because they do not correct the language of the base claim.

Claims 37 is directed to the correction of a genetic defect by activation of a silent gene through changes in its methylation pattern caused by inhibition of demethylase. Because of lack of written description; see the above rejection, to make and use the claimed invention necessitates undue experimentation. Factors to be considered in determining whether undue experimentation is required are summarized *In re* Wands [858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)]. The Wands factors are: (a) the quantity of experimentation necessary, (b) the amount of direction or guidance presented, (c) the presence or absence of working example, (d) the nature of the invention, (e) the state of the prior art, (f) the relative skill of those in the art, (g) the predictability or unpredictability of the art, and (h) the breadth of the claim.

The nature and breadth of the claimed invention encompasses identifying which silent genes are related to the genetic defects and activation of said genes by changing their methylation pattern through inhibiting DNA demethylase. Furthermore, the nature and breath of the invention comprises finding the very change in metylation pattern of said silent gene that would turn it on.

The necessary experimenation has very low probability of success, because, taking into account that several tens of thousands of genes are expressed in human body, one skilled in the art cannot predict, or easily find, what phenotype effects are related to the lack of expression of certain gene. Applicants do not provide any guidance or example of a genetic defect that is related to suppression of a certain gene. In addition, Applicants do not identify any genetic defect in the specification; neither the Applicants show any change in the methylation pattern of any gene; neither Applicants demonstrate that any silent gene can be activated by changes of its methylation pattern caused by inhibition of demethylase. Actually, because demethylation of cytosine residues turns the gene into an active one, it seems that inhibiting demethylase would prevent demethylation of said silent gene, thus said gene would still remain silent. Hence, one skilled in the art concludes that claim 37 is not directed to the intended invention.

In conclusion, Applicants fails to provide the guidance and examples how to make and use the invention so that it works, as intended, without undue experimentation.

5. Conclusion

No claim is in condition for allowance, however the application contains allowable subject matter. The following is examiner reason for indicating allowable subject matter. Applicants were the first to discover human DNA demethylase consisting of amino acid residues 150-411 of SEQ ID NO:2 and encoding DNA. SEQ ID NO: 2 was first disclosed by Hendrich et al., as methyl–CpG binding protein, Accession No. AF072242, with priority Oct. 28, 1998; see the enclosed copy. However, Applicants were the first who demonstrated its function by presenting the details of the enzymatic reaction.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Malgorzata A. Walicka, Ph.D., whose telephone number is (703) 305-7270. The examiner can normally be reached Monday-Friday from 10:00 a.m. to 4:30 p.m.

If attempts to reach examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, Ph.D. can be reached on (703) 308-3804. The fax phone number for this Group is (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionists whose telephone number is (703) 308-0196.

Malgorzata A. Walicka, Ph.D.

Patent Examiner

Art Unit 1652

TEKCHAND SAIDHA
PRIMARY EXAMINER